REMARKS

The Office Action contained one rejection of the claims under 35 USC §112 and one rejection of the claims under 35 USC §103. Each will be responded to below.

a. Response to §112 Rejection

Claims 1, 5 and 10 were rejected under 35 USC §112, second paragraph, as being indefinite, on grounds that the phrase "antimicrobial compound" had not been amended or deleted in all instances.

Accordingly, by the present amendment, Applicant has corrected claims 1, 5 and 10 to recite --macrolide antibiotic-- in place of "antimicrobial compound" in all instances. Specifically, amendments have been made at claim 1, lines 7 and 10, claim 5, line 3, and claim 10, line 6.

b. Response to §103 Rejection

Claims 1-3, 5-10 and 12-23 were rejected under 35 USC §103(a) over Crandall (U.S. 5,560,910) in view of Dawson (U.S. 6,239,113).

Applicant respectfully traverses the rejection. In order to establish a *prima facie* case of obviousness, there must be both (i) some suggestion or motivation in the prior art to modify the reference or combine the references, and (ii) there must be a reasonable expectation of success (MPEP 2143). For the reasons discussed below, the cited art provides neither the motivation nor expectation of success required to support the rejection.

i. Cited art does not provide required motivation

In the Office Action, it is asserted that Dawson teaches topical application of an azilide antibiotic at a sufficient rate for "penetration of the conjunctiva and the cornea", and that

motivation to use the lecithin organogel of Crandall "would have arisen because such a combination would have allowed sufficient delivery of the antibiotic to the eyelids."

Applicant respectfully disagrees. The tissues of the eye to which the treatment of Dawson is directed are membranes, ducts, glands and sacks that are bathed in the fluids of the eye. In particular, the conjunctiva is a thin mucous membrane, and the cornea is likewise a thin (500 micron), membranous structure, that is highly permeable and constantly wetted with fluid (tears). In Dawson, therefore, the antibiotic is diffused into these tissues primarily by water, mainly by using an aqueous solution.

Dawson does not, however, provide any motivation for penetrating into subdermal tissues (e.g., ligaments and muscles) underlying the skin. The conditions described in Dawson involve the ducts, sacks and membranes that are reached without penetrating the dermal layers. In the case of the eyelid, the conditions referred to in Dawson involve the conjunctiva and the glands/hair follicles along the edges of the lid, rather than subdermal tissues. Furthermore, although Dawson lists many compounds that may be included in the solution with the hasilide antibiotic, including polymeric agents for maintaining the antibiotic in suspension, penetrating agents are not included or contemplated.

Unlike the ocular tissues involved in Dawson, the skin presents a formidable barrier to penetration by drugs. The skin is composed of the epidermis, dermis and subcutaneous tissues. The surface of the skin is tough and dry, and the stratum corneum of the epidermis is particularly impermeable. The aqueous action would be incapable of penetrating the skin and reaching into the underlying tendons and muscles, which lie millimeters or even centimeters below the surface, rather than microns in the ocular tissues involved in Dawson. Moreover, Dawson shows no recognition of inflammation being caused by microbial action in these deep tissues or any other reason for penetrating through and below the skin.

In short, Dawson does not teach or suggest penetrating an azilide antibiotic through a person's skin and into underlying soft tissues such as muscles and ligaments. Furthermore, the reference states nothing concerning treatment of inflammations in a subdermal musculoskeletal tissue. The reference therefore provides no motivation for combining the azilide antibiotic with a penetrating agent so as to reach such tissues, as is required by Applicant's claims.

It should be also be noted that lecithin organogels are widely considered unsuitable for use in the eye, as they cause irritation and may function by disrupting the structure of the tissue. This would further mitigate against the obviousness of the proposed combination of Dawson with Crandall.

c. Cited art does not provide required expectation of success

As was discussed in Applicant's prior response, Crandall teaches that a proteolytic enzyme may be used with a penetrating agent. However, the proteolytic enzymes of Crandall bear no structural resemblance whatsoever to macrolide antibiotics. Proteolytic enzymes are comparatively simple compounds with mostly chain-like structures, whereas macrolide antibiotics are complex compounds that include large macrocyclic rings and ancillary ring structures. Given these profound structural dissimililarities, one of ordinary skill in the art would not have had a reasonable expectation of success for the use of a macrolide antibiotic in the compositions that are taught by Crandall.

Dawson is silent on the use of penetrating agents and lecithin organogels, and adds nothing that would suggest that macrolide antibiotics could be use successfully therein to penetrate to subdermal musculoskeletal tissues.

d. Conclusion

For the reasons discussed above, the cited art fails to provide any suggestion or motivation for using a macrolide antibiotic in the compositions of Crandall, and also fails to provide any reasonable expectation of success for such use. The Office Action therefore fails to establish a *prima facie* case of obviousness against Applicant's claims. Applicant therefore respectfully requests that the rejection of the claims under 35 USC §103 be reconsidered and withdrawn.

Applicant respectfully requests reconsideration of the present application in view of the amendments and remarks set forth herein. It is believed that the above-referenced claims are now in condition for allowance. If there is any matter that can be expedited by consultation with

Applicant's attorney, such would be welcome. Applicant's attorney can normally be reached at the telephone number given below.

Signed at Bellingham, County of Whatcom, State of Washington this 16th day of January 2003.

Respectfully submitted,

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CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date shown below.

Dale Y Perez
(Print name of person mailing paper)

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Dale Y Perez
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VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A method for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said method comprising the steps of:

providing a treatment composition comprising, in combination:

(i) a selected macrolide antibiotic; and

(ii) a selected mobilizing agent in an amount sufficient to enable said [antimicrobial compound] macrolide antibiotic to penetrate into said sub-dermal soft tissue; and

applying said treatment composition to said predetermined area of the body so that said [antimicrobial compound] macrolide antibiotic penetrates said sub-dermal soft tissue so as to reach said microbial infection therein.

5. (amended) The method of claim 1, wherein the step of providing said treatment composition comprises:

selecting said [antimicrobial compound] macrolide antibiotic from the group consisting of azithromycin, erythromycin and roxithromycin.

10. (amended) A treatment composition for alleviating a disease state resulting from a microbial infection affecting sub-dermal soft tissue in a predetermined area of the body, said treatment composition comprising:

(i) a selected macrolide antibiotic; and

(ii) a selected mobilizing agent in an amount sufficient to enable said [antimicrobial compound] macrolide antibiotic to penetrate into said sub-dermal soft tissue so as to reach said microbial infection therein when said composition is applied to said predetermined area of the body.